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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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FEB 23 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT:

Of-anol 5% Granular, EPA Reg. #3125-330, and 1.5% Granular, 3125-331; Caswell # 447AB; Project # 8-0376; Cord Nos. 208706, 208707

TO:

William H. Miller
Product Manager (16)
Registration Division (TS-767C)

FROM:

James N. Rowe, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division/HED (TS-769C)

THRU:

Quang Q. Bui, Ph.D., D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)
and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

ACTION: Request expansion of Of-anol's present use on turf grass (Granular formulations 5% and 1.5%) to cover uses on other non-crop areas such as fence rows and roadsides, ornamentals and nurseries and soil mix for ornamentals including potting soil mix.

RECOMMENDATIONS:

The expansion of Of-anol use to cover other non-food uses cannot be toxicologically supported at the present time. Additional data requested from the test laboratory which performed the previously reviewed subchronic delayed neurotoxicity study in hens must be submitted (see conclusions below). The 21-day dermal study has been reviewed and is acceptable.

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Review

1) Subchronic delayed neurotoxicity study in hens

This study has been previously reviewed (D.E.R. dated 9/2/86; Mobay report # 90231). Findings from the study are as follows:

Based on the significant depressions in body weight and cholinesterase activity at the high dose, without any evidence of neuronal degeneration--as determined by no change in gait at any dose level during the course of the study and no apparent histopathological changes at the high dose level--isofenphos does not appear to produce delayed neurotoxicity. The tentative delayed neurotoxicity NOEL is set at >2 mg/kg (HDT). The slight, consistent nerve degeneration observed in the spinal cord of the vehicle control and high dose groups is stated in the report to be the result "of the conventional husbandry of these chickens, which had been commercially used before the study". The reviewer is concerned that these findings could mask any subtle effect of isofenphos. Therefore, it is requested that additional data be submitted to substantiate that this is a normal background neuropathological change in chickens.

The study is designated as Core Supplementary data. It may be upgraded upon submission and approval of the requested additional data.

2) The submitted 21-day dermal rabbit study has been reviewed and the D.E.R. is attached (report # 339-113). The findings of the study are noted below:

Based on the absence of dermal irritation at any dose level, in either sex, a dermal irritation NOEL is set at the HDT of 253.0 mg/kg/day. Based upon statistically significant depressions in plasma ChE in both male and female rabbits at the mid and high dose level, a plasma ChE inhibition NOEL of 50 mg/kg/day (LDT) is determined. A RBC and brain ChE inhibition NOEL is set at 253 mg/kg/day (HDT).

This study is designated Core Minimum data.

Conclusions:

The registrant's request to expand Oftanol registered use on turf grass to cover ornamentals and nurseries, and certain other non-crop areas cannot be toxicologically supported at the present time until the following additional data for the subchronic delayed neurotoxicity hen study is submitted:

* evidence that the slight, consistent nerve degeneration observed in the spinal cord of the vehicle control and high dose groups (as stated in the report) is the result "of the conventional husbandry of these chickens, which had been commercially used before the study".

Reviewed by: James N. Rowe, Ph.D. *James N. Rowe*
Section V, Tox. Branch (TS-769C) 2122151
Secondary reviewer: Quang O. Bui, Ph.D.
Section V, Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: 21-Day dermal (§82-2)

TCX. CHEM. NO.: 447AB

ACCESSION NUMBER: 40217401

MRID NO.: N/A

TEST MATERIAL: Oftanol 5G

SYNONYMS:

STUDY NUMBER(S): 339-113

SPONSOR: Mobay Corporation, Health, Environment and Safety, Corporate Toxicology Department, 17745 S. Metcalf Avenue, Stilwell, Kansas 66085

TESTING FACILITY: Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia 22180

TITLE OF REPORT: 21-day dermal toxicity study with Oftanol 5G in rabbits

AUTHOR(S): D.E. Bailey, Ph.D

REPORT ISSUED: September 18, 1986

CONCLUSIONS:

Based on the absence of dermal irritation at any dose level, in either sex, a dermal irritation NOEL is set at the HDT of 253.0 mg/kg/day. Based upon statistically significant depressions in plasma ChE in both male and female rabbits at the mid and high dose level, a plasma ChE inhibition NOEL of 50 mg/kg/day (LDT) is determined. A RBC and brain ChE inhibition NOEL is set at 253 mg/kg/day (HDT).

This study is designated Core Minimum data.

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METHODS:

A photocopy of the experimental methods is attached. The following comments are noted:

- 1) The powder applied topically was not moistened as recommended by the EPA guidelines.
- 2) The assumption is made (p. 2) that the material, Oftanol 5G, is 100% pure for the purpose of dosage calculations. Since the material is known to contain 5% of the active ingredient, the actual dosages applied are (stated dosage) x (0.05) = 50 (1000), 112.5 (2250) and 253 (5060) mg/kg/day.

RESULTS:

Body weights/gains

Oftanol 5G had no effect upon mean body weights or body weight gains during the test period in either the male or female rabbits.

Food consumption

No statistically significant depression in mean food consumption or total food consumption occurred during the treatment period as a result of Oftanol 5G dermal exposure.

Dermal irritation

Neither male or female skin in the controls or treated groups gave evidence of dermal irritation (erythema and eschar formation, edema) during the three weeks of exposure to the test compound.

Hematology/clinical chemistries

Minor effects upon blood or clinical biochemistry parameters were reported (see table T-1 of selected values below).

Segmented neutrophils and basophils were statistically significantly lower ($p < 0.05$) in females and males, respectively.

Globulin values were lower in the mid and high dose groups (statistically significant negative trend, $p < 0.05$) of treated males as compared to the controls. Both phosphorus and blood urea nitrogen levels were elevated (statistically significant, $p < 0.05$) in females of the high dose group as compared to the controls. This elevation in P and BUN, in conjunction with the suggestion of increased histopathological findings in the kidneys, would seem to confirm that some impairment of kidney function may be occurring in the females in the HDT.

T-1 Selected hematology/clinical parameters

mg/kg	Hematology		Clinical chemistry		
	SEG (TH/UL)	BASO (TH/UL)	Globulin (G/DL)	Phosphorus (MG/DL)	BUN (MG/DL)
†					
0	2.4(2.09) ^a	0.4(0.17)	1.4(0.11)	7.0(0.47)	18(2.8)
50	2.6(1.43)	0.2(0.11)	1.4(0.29)	7.4(0.33)	19(1.9)
112.5	1.5(0.57)	0.3(0.08)	1.1(0.10)	6.6(0.67)	17(3.6)
253.0	1.8(0.81)	0.1*(.11)	1.2(0.09)	7.4(0.48)	19(4.2)
‡					
0	2.0(0.74)	0.3(0.08)	1.2(0.24)	6.5(0.66)	21(3.1)
50	2.2(0.89)	0.3(0.15)	1.4(0.30)	6.6(0.22)	20(1.5)
112.5	1.0(0.39)	0.3(0.11)	1.3(0.16)	6.9(0.62)	20(1.1)
253.0	0.9*(.61)	0.2(0.08)	1.3(0.29)	7.7*(.43)	24*(1.2)

^a mean (S.D.)§ significantly negative trend for females ($p < 0.05$)¶ significantly positive trend for females ($p < 0.05$)† significantly negative trend for males ($p < 0.05$)* significantly different from control value ($p < 0.05$)Organ weights(g)/ratios (%)

No changes in organ weights or organ weight ratios were observed among any dose group of either male or female rabbits.

Gross/histopathology (Table T-2)

No gross necropsy findings of a compound-related nature were reported for any dose group of male or female rabbits.

There is a suggestion in females that the kidney may be slightly affected by dermal exposure to Oftanol 5G in the high dose group as compared to the control group. In the control females, only 2/5 animals are reported with some kidney findings as opposed to 3/5 in the high dose group. There are twice the total number of changes (5 vs. 10) in the treated as control animals. In addition to focal mononuclear infiltration, regenerative tubular epithelium and cortical fibrosis/scars, which are observed in the controls (slight or minimal vs. slight to moderate or minimal in treated), chronic interstitial nephritis (slight) is observed in 3/5 of HDT as opposed to 0/5 in control females.

T-2 Histopathology for the kidneys (females)Controls

<u>Animal #</u>	<u>Finding</u>
E 40411	- focal mononuclear infiltration--slight - regenerative tubular epithelium--slight - cortical fibrosis/scars--minimal
E 40412	- tubular cell vacuolation--minimal - regenerative tubular epithelium--minimal
E 40413	-----
E 40414	-----
E 40415	-----

High dose

E 40441	-----
E 40442	-----
E 40443	- focal mononuclear infiltration--moderate - regenerative tubular epithelium--moderate - cortical fibrosis/scars--moderate - chronic interstitial nephritis--moderate
E 40444	- focal mononuclear infiltration--slight - regenerative tubular epithelium--slight - chronic interstitial nephritis--slight
E 40445	- focal mononuclear infiltration--slight - regenerative tubular epithelium--minimal - chronic interstitial nephritis--slight

Cholinesterase activity (table T-3)

RBC and plasma cholinesterase activities were affected by dermal application of Oftanol 5G.

RBC ChE activity appears to be depressed somewhat in the HDT group males as compared to the control values in Week 2 and 3 (81 and 76% of concurrent control values, not statistically significant).

In females, there is a statistically significant negative trend of depressed activities in the compound-treated groups as compared to controls at Week 2. Week 3 values are similar (as % of concurrent control; not statistically significant). The biological significance of these findings is questionable since the concurrent control values for Weeks 2 and 3 vary so much from either the initial ChE activities in pretreatment or week 1 values.

T-3 Cholinesterase (RBC, Plasma) values (from table 5 of report)

RBC ChE:

Dose Pretreatment
group^c (umol/ml)

Week 1

Week 2

Week 3

Males

1	9.3(1.13) ^a	9.4(0.72)/100	10.1(1.11)/100	10.1(1.18)/100
2	9.4(2.10)	9.5(1.53)/101 ^b	9.8(1.36)/ 97	9.1(2.08)/ 90
3	10.5(1.40)	9.6(0.62)/102	9.4(1.11)/ 93	9.2(0.58)/ 91
4	9.0(1.40)	8.6(1.16)/ 92	8.2(1.49)/ 81	7.6(1.92)/ 76

Females

(XX)

1	8.3(1.38)	8.5(1.52)/100	9.9(0.88)/100	8.9(0.82)/100
2	7.5(1.06)	7.9(1.86)/ 92	8.8(1.08)/ 89	7.9(1.75)/ 89
3	7.5(1.88)	7.4(1.43)/ 87	<u>7.9(1.60)/ 80</u>	7.0(1.70)/ 79
4	8.3(1.17)	8.7(1.36)/102	<u>8.3(1.01)/ 84</u>	7.6(1.19)/ 85

PLASMA ChE

Males

(XXX)

1	2.8(0.38)	2.6(0.32)/100	2.0(0.34)/100	2.8(0.34)/100
2	3.5(0.63)	2.8(0.40)/108	3.0(0.58)/150	<u>2.7(0.43)/ 95</u>
3	2.6(0.28)	* <u>2.0(0.20)/ 79</u>	2.4(0.31)/119	*2.3(0.33)/ 81
4	2.8(0.41)	<u>2.2(0.40)/ 83</u>	2.5(0.31)/124	* <u>2.3(0.25)/ 81</u>

Females

(XX)

(XX)

(XXX)

1	3.2(0.15)	2.8(0.22)/100	3.0(0.12)/100	2.9(0.14)/100
2	3.3(0.86)	2.6(0.22)/ 91	2.8(0.69)/ 94	*2.7(0.73)/ 93
3	3.3(0.74)	<u>2.3(0.42)/ 81</u>	<u>2.4(0.69)/ 81</u>	* <u>2.4(0.46)/ 84</u>
4	3.1(0.45)	<u>2.2(0.29)/ 80</u>	2.4(0.41)/ 81	* <u>2.4(0.29)/ 82</u>

^a mean (standard deviation)^b average percent activity (treated) mean concurrent control enzyme activity; ^c respective doses of 0, 50, 112.5, 253 mg/kg/day: values are indicative of a significant difference from control value-($p \leq 0.05$) when statistically analyzed utilizing pretreatment values as the covariate* significantly different from concurrent control value ($p \leq 0.05$)(XX) significantly negative trend in females ($p \leq 0.05$)(XXX) significantly negative trend in males and females ($p \leq 0.05$)

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Plasma ChE activities in males were consistently lower (statistically significant, $p < 0.05$) than pretreatment values in the mid or high dose groups, or concurrent control values, at Week 1 or Week 3. Week 2 values were somewhat lower than the preinitiation values but much higher than the concurrent control values which were significantly depressed as compared to other time periods (e.g. Week 2 control = 2.0 vs Week 1 control = 2.6 or Week 3 = 2.8).

Female plasma ChE values were similarly depressed (around 80% of concurrent control values) at the mid and high dose levels for all three weeks on test. Generally, these values were statistically significantly lower than pretreatment activities and for Week 3 they were also significantly lower than the concurrent controls.

No effects of Oftanol 5G upon brain ChE were noted at any dose level as compared to control treatment.

SUMMARY/CONCLUSIONS:

Dermal application of Oftanol 5G powder at actual calculated active ingredient concentrations of 50, 112.5 and 253 mg/kg/day to male and female rabbits for three weeks produced no evidence of any dermal irritation, depression in body weights/body weight gains, decrease in food consumption, changes in organ weights (kidneys, testes, liver) or gross pathology. A small impairment of kidney function in the high dose females is suggested based on a small increase in histopathology changes (intensity, type) and a statistically significant elevation in serum phosphorus and blood urea nitrogen.

Plasma cholinesterase activities were affected at the mid and high dose levels (depression of approximately 20% of concurrent control values; generally statistically significant for either trends in activity, comparison against pretreatment values or concurrent control values) in both male and female rabbits. No consistent effects upon RBC or brain ChE were apparent.

Based on the absence of dermal irritation at any dose level, in either sex, a dermal irritation NOEL is set at the HDT of 253.0 mg/kg/day. Based upon statistically significant depressions in plasma ChE in both male and female rabbits at the mid and high dose level, a plasma ChE inhibition NOEL of 50 mg/kg/day (LDT) is determined. A RBC and brain ChE inhibition NOEL is set at 253 mg/kg/day (HDT).

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

REVIEWER

006607

SEP - 2 1986

005435

MEMORANDUM

SUBJECT: Isofenphos Subchronic Delayed Neurotoxicity Study; Mobay report # 90231; Caswell # 447AB; Project # 128

TO: William H. Miller
Product Manager (16)
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division/HED (TS-769C)

James N. Rowe
9/29/86

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)
and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

W.H. Rowe
9/2/86

ACTION: Review isofenphos subchronic neurotoxicity study entitled, " Study for Subchronic Neurotoxicity (90-Day Study with Chickens)"; submitted by Mobay Chemical Corporation as study # 90231; A 258563, 073466; Cas.# 447AB; EPA I.D. 3125-326

RECOMMENDATIONS:

Based on the significant depressions in body weight and cholinesterase activity at the high dose, without any evidence of neuronal degeneration—as determined by no change in gait at any dose level during the course of the study and no apparent histopathological changes at the high dose level—isoferphos does not appear to produce delayed neurotoxicity. The tentative delayed neurotoxicity NOEL is set at >2 mg/kg (HDT). The slight, consistent nerve degeneration observed in the spinal cord of the vehicle control and high dose groups is stated in the report to be the result "of the conventional husbandry of these chickens, which had been commercially used before the study". The reviewer is concerned that these findings could mask any subtle effect of isofenphos. Therefore, it is requested that additional data be submitted to substantiate that this is a normal background neuropathological change in chickens.

This study is designated as Core Supplementary data. It may be upgraded upon submission and approval of the requested additional data.

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DATA EVALUATION RECORD

STUDY/ACTION TYPE: Subchronic delayed neurotoxicity in White Leghorn hens

CHEMICAL: Isofenphos: 1-methylethyl 2-[[ethoxy[(1-methylethyl)amino] phosphi-
nothioyl] oxy]benzoate

TEST MATERIAL: Technical Cftanol; batch no. 0005281 (Mobay Chemical Corpora-
tion); purity 92.5% (communication of Mobay Chemical Corporation of 7/16/84);
test compound was refrigerated at a temperature of 8° - 13°C

STUDY I.D.:

1. Title: " Study for Subchronic Neurotoxicity (90-Day Study with Chickens)"
2. Laboratory: Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, West Germany
3. Sponsor: Mobay Chemical Corporation, Agricultural Chemicals Division, Kansas City, Mo. 64120
4. Study #: T 7017 964
5. Date of Report: 5/13/85
6. Study Director: Dr. W. Flucke
7. Caswell # 447AB, Accession 258563 073466; EPA ID # 3125-326

METHODS:

A photocopy of the methods section is appended. The following comments are noted:

1. The age of the hens was given as 15-20-months old which is not optimum for testing for delayed neurotoxicity, the EPA recommended age being between 8-14 months of age.
2. The solubility of Isofenphos in water is approximately 20 ppm, therefore the homogeneity of the material in an aqueous vehicle was of concern. The report presented data (pgs. 45-48) on the compound's homogeneity in 2% Cremophor/water indicating that at various concentrations(0.001 to 1.0 %) the material was of an adequate homogeneous nature (82 to 98% of specified value).
3. The pilot study (Section 3.4 of methods) was discussed but not submitted.

RESULTS:

1. Clinical signs/symptoms; mortality

In general, there were no unusual clinical observations except for one animal (no. 19) in the vehicle control which exhibited a waddling gait from day 14 onwards and which was sacrificed on day 30. In addition, a high dose animal (no.

44) was reported as apathetic with reduced mobility on day 4 and dying on day 5 of the test.

2. Body weights : Table 1 (see below)

Isofenphos statistically significantly reduced ($p < 0.05$ and/or $p < 0.01$) body weights when compared against the vehicle controls (1.50 kg/high dose vs 1.73 kg/control) by the end of week 1 of administration and this depression in body weight continued through week 13 of the study. The positive delayed neurotoxic control (TOCP) also reduced the mean body weights from week 11 on, although the depression in weight was not statistically significant.

Table 1: Body weight means (kg)

Dose group	W0	W1	W2	W3	W4	W5 ...	W11	W12	W13
I(0 mg/kg)	1.87	1.81	1.80	1.79	1.85	1.86	1.66	1.63	1.60
II(0 mg/kg: vehicle)	1.79	1.73	1.74	1.80	1.84	1.82	1.79	1.74	1.70
V(2 mg/kg)	1.72	1.50*	1.51†	1.55†	1.58†	1.63*	1.52†	1.50*	1.55
VI(TOCP)	1.79	1.74	1.73	1.74	1.70	1.70	1.57	1.54	1.54

W= week on test; *significantly different from vehicle control ($p < 0.05$); † significantly different from vehicle control ($p < 0.01$)

3. Forced motor activity: shooing and ladder climbing

Shooing: A slightly abnormal gait (grade no.1) or ataxia (grade no. 2) was observed only during week 7 or 8 in all the isofenphos groups which was not dose-related and the animals did not continue to exhibit this effect on mobility. The authors reported that this was due to an over vigorous shooing of the hens dosed with isofenphos. The TOCP control group showed decreased or aberrant mobility by the beginning of week 4 which grew progressively more pronounced through week 13 (grade 1 effect/2 animals for week 4; primarily grade 2 by week 13 in all animals). One animal in the positive control group had severe ataxia by week 9 which continued throughout the rest of the test period (animal no. 52).

Ladder climbing: No statistically significant variations in the forced ladder climbing times among any of the groups was reported. Chicken no. 52 of the TOCP group showed severe ataxia from week 9 onwards and was reported to repeatedly refuse to climb the ladder due to severe impairment of motor coordination.

4. Cholinesterase activities: Table 2 (see below)

Cholinesterase activities in blood plasma, erythrocytes (RBCs) and whole blood were examined. Plasma cholinesterase (pseudocholinesterase) was statistically significantly inhibited on day 26 of sampling at the 1 and 2 mg/kg doses compared to the vehicle control (0.52 U/ml = mid, 0.39 U/ml = high vs 1.10 U/ml, vehicle control).

There was also depressed cholinesterase activities in the RBCs (true cholinesterase) at day 26 of test (statistically significant only at high dose) as well as the depressed cholinesterase in whole blood at both day 55 (statistically significant at both dose levels) and day 83 on test (lower but not statistically significant at both doses). The TOCP controls showed somewhat lower plasma and RBC cholinesterase activities at day 26 than the vehicle controls (0.76 and 0.33 U/ml in treated, respectively, vs. 1.10 and 0.38 U/ml, respectively in controls). No apparent effect on cholinesterase activity in whole blood in the positive control group was evident.

Table 2: mean cholinesterase activity (U/ml)

Dose group	Plasma(day 26)	Erythrocyte(day 26)	Whole Blood		
			d0	d55	d83
I(0 mg/kg)	0.78	0.45	0.67	0.63	0.55
II(0 mg/kg: vehicle)	1.10	0.38	0.72	0.61	0.55
III(0.25 mg/kg)	0.82	0.36	0.73	0.59	0.58
IV(1.00 mg/kg)	0.52†	0.33	0.73	0.46*	0.51
V(2 mg/kg)	0.39*	0.29*	0.65	0.39*	0.44
VI(TOCP)	0.76	0.33	0.75	0.68	0.65

d= day of test; * significantly different from vehicle control ($p < 0.05$); † significantly different from vehicle control ($p < 0.01$)

5. Gross necropsy/ histopathology

Gross necropsy: No differences in gross pathology were noted when the controls were compared against the treatment groups.

Histopathology: The vehicle control, high dose and positive control groups were examined for microscopic findings (tables on pages 39-41 of the report).

There were no unusual differences in the histology for the vehicle control group and the high dose group. Both groups showed a consistent lympho-histiocytic infiltration in the sciatic nerve, lumbar and medulla oblongata/cerebellar nerve sections which was suggested by the study author to be a normal observation in commercially used chickens. Generally slight degeneration was observed in both the control and high dose group thoracic (9/10 vs 9/10, respectively) and cervical (7/10 vs 7/10, respectively) nerve sections. One animal in the high dose group had autolyzed nerve tissue which prevented meaningful histological examination.

In contrast to the high dose group, the TOCP positive control had generally moderate to severe nerve degeneration in the lumbar, thoracic and cervical nerves of the spinal cord as well as slight to moderate nerve degeneration in the medulla oblongata/cerebellum in all animals. This is in contrast to the previously

mentioned slight nerve degeneration observed in the cervical and lumbar nerves of the vehicle control animals. Lympho-histiocytic infiltration of the sciatic nerve was also a consistent finding in the positive controls.

CONCLUSIONS/RECOMMENDATIONS:

The mid and high doses of isofenphos administered were adequate to induce some systemic toxicity. Isofenphos produced a statistically significant depression in mean body weights at the high dose level (2 mg/kg) in week 1 on test and this depression continued throughout the period of test compound administration. The test compound also produced a statistically significant inhibition in plasma cholinesterase on day 26 of blood sampling in both the mid (1 mg/kg) and high dose groups (2 mg/kg) as well as depressed RBC cholinesterase activity at day 26 and depressed cholinesterase in whole blood at both day 55 (statistically significant at both dose levels) and day 83 on test (not statistically significant at both doses).

In contrast to the positive control (TOCP), which elicited ataxia in all animals by week 13 on test, no isofenphos-related effects on motor coordination were observed during forced motor activity (shooping). No compound-related histopathology was observed in the high dose group as compared to the vehicle control, although there was some evidence of slight nerve degeneration of the thoracic and cervical nerve fibers in both the control and high dose animals. The positive control produced the expected neural degeneration indicative of its delayed neurotoxicity in both the peripheral and central neurons. This indicates the responsiveness of the test animals to a delayed neurotoxicant.

Based on the significant depressions in body weight and cholinesterase activity at the high dose, without any evidence of neuronal degeneration—as determined by no change in gait at any dose level during the course of the study and no apparent histopathological changes at the high dose level—isoferphos does not appear to produce delayed neurotoxicity. The tentative delayed neurotoxicity NOEL is set at >2 mg/kg (HDT). The slight, consistent nerve degeneration observed in the spinal cord of the vehicle control and high dose groups is stated in the report to be the result "of the conventional husbandry of these chickens, which had been commercially used before the study". The reviewer is concerned that these findings could mask any subtle effect of isofenphos. Therefore, it is requested that additional data be submitted to substantiate that this is a normal background neuropathological change in chickens.

This study is designated as Core Supplementary data. It may be upgraded upon submission and approval of the requested additional data.

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Pages 24 through 29 are not included in this copy.

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